REMARKS

I. Request for Continued Examination

A Final Action, dated April 21, 2005, was issued in the present application (Application No. 09/457,421). Applicants respectfully submit herewith a Request for Continued Examination (37 C.F.R. 1.114).

II. Status of the Claims

Claims 1-16 were canceled in a Preliminary Amendment submitted September 04, 2003. Claims 17-25 were canceled in an Amendment and Response to Restriction Requirement submitted October 14, 2003. Claims 34-36 were amended and new claim 40 was added in an Amendment submitted February 18, 2004. Claims 26 and 30 were amended and new claim 41 was added in an Amendment submitted June 18, 2004. Claims 26, 28, 35, 36, and 39 were amended and claims 27 and 41 were canceled in the Amendment submitted December 20, 2004. No claims have been amended, canceled or added in the Amendment submitted herewith. Claims 26 and 28-40 are therefore presently pending in the application.

III. Claims Rejected Under 35 U.S.C. § 103

The Action maintains the rejection of claims 26 and 28-40 under 35 U.S.C. § 103 as allegedly being unpatentable over Hung *et al.* (*Nat Immun Cell Growth Regul*, 9(3):160-164, 1990) in view of Davis *et al.* (U.S. Patent 4,920,209) and the rejection of claims 26, 28-31 and 33-40 under 35 U.S.C. § 103 as allegedly being unpatentable over Chanda *et al.*, 1990 (*Int. Rev. Immunol.*, 7(1):67-77, 1990) in view of Davis *et al.* (U.S. Patent 4,920,209).

In the previous Official Action (mailed September 22, 2004), the Examiner asserted that Hung *et al.* taught an immunogenic composition of the presently claimed invention (*i.e.*, claim 26) and that one of skill in the art would have been motivated at the time the invention was made to administer the composition to a human and "experiment" with the methodologies to arrive at a prime-boost regimen. The Action additionally rejected the

dependent claims alleging that it would have been obvious to one of skill in the art to: (a) administer booster env and/or gag protein subunits, (b) "experiment" with the subunit antigen dosage amounts, (c) insert the *rev* gene in frame and after the *env* gene but before the poly-A signal sequence and (d) select the appropriate HIV-1 strains. The Action further alleged that Davis *et al.* taught the deletion of both the E1 and E3 regions which can be used in connection with the adenovirus having a deletion in the E3 region taught by Hung *et al.*

The Examiner also alleged in the previous Official Action (mailed September 22, 2004), that Chanda *et al.* taught an immunogenic composition comprising a recombinant adenovirus construct of the present invention and that one of skill in the art at the time the invention was made would have been motivated to administer this vaccine to a human to induce an immune response against HIV-1 infection. The Action also rejected the dependent claims, stating that it would have been obvious to one of skill in the art to: (a) "experiment" with various methodologies of administering the composition, such as prime-boost methods, (b) administer to the subject intramuscular injections of the env and/or gag polypeptide, (c) "experiment" with the antigen dose amounts to determine the optimal dosage to optimize an immune response, (d) "experiment" with the location of the *rev* gene in relation to the *env* gene, (e) select the appropriate HIV-1 strains such as LAV and MN, and (f) "experiment" with the dosage amount of virus for a specific group of subjects. The Action further alleged that Davis *et al.* taught the deletion of both the E1 and E3 regions which can be used in connection with the adenovirus having a deletion in the E3 region taught by Chanda *et al.*

In Response to the Official Action, mailed December 20, 2004, Applicants submitted: (i) that the Hung *et al.* reference described a recombinant adenovirus type 7 (Ad7) construct comprising a gene expressing either the hepatitis B surface antigen (HBsAg) or the human immunodeficiency virus type 1 envelope glycoprotein (*env*), (ii) that Hung *et al.* demonstrated that the Ad7-HBsAg construct was propagated in cultured cells and that propagation of the Ad7-*env* construct in cultured cells required co-infection with an Ad7 construct expressing the HIV-1 *rev* gene and (iii) that Hung *et al.* demonstrated that intra-

tracheal inoculation of dogs with the Ad7-HBsAg (hepatitis B) construct induced an antibody response. Similar studies in dogs (nor any other mammals) were not performed with the Ad7-*env* construct.

Applicants therefore asserted that Hung *et al.* provided no *in vivo* data or description to suggest to one of skill in the art that an Ad7-*env* construct would in fact elicit an immune response in any mammal and that Hung *et al.* did not teach or suggest administering any booster dosages of the recombinant adenovirus as presently claimed, and as such, submitted that Hung *et al.* did not teach nor describe the presently claimed prime-boost method for producing an immune response against HIV-1 infection in a human.

Applicants also submitted in Response to the Official Action mailed December 20, 2004: (i) that the Chanda *et al.* reference described a recombinant Ad7 construct comprising the HIV-1 *env* gene (Ad7-*env*), the major late promoter (MLP), the tripartite leader (TPL) and a poly-A sequence, (ii) that Chanda *et al.* also described a second Ad7 construct comprising both the *env* and *rev* genes (Ad7-*rev-env*), (iii) that Chanda *et al.* demonstrated that the env protein is expressed in A549 and HEK cells infected with Ad7-*env* or Ad7-*rev-env*, and (iv) that Chanda *et al.* immunized dogs with an Ad7 construct expressing hepatitis B surface antigen (HbsAg, *i.e.*, an Ad7-HbsAg construct) and observed an anti-HBs response, stating that "the data demonstrate that under semi-permissive conditions, adenovirus vectors may induce seroconversion to products of foreign gene inserts". Chanda *et al.* did not perform a similar study in dogs (or any other mammal) with the Ad7-*env* or Ad7-*env-rev* constructs.

Applicants therefore asserted that the Chanda *et al.* reference had no *in vivo* data or description to suggest to one of skill in the art that an Ad7-*env* construct would in fact elicit an immune response in any mammal and that Chanda *et al.* did not teach or suggest administering any booster dosages of the recombinant adenovirus as presently claimed, and as such, submitted that Chanda *et al.* did not teach nor describe the presently claimed adenovirus vectored prime-boost method for producing an immune response against HIV-1 infection in a human.

In contrast, Applicants' data set forth in the present invention clearly demonstrates that the claimed adenovirus constructs (i) are immunogenic in mammals (*e.g.*, both dogs and non-human primates (*i.e.*, chimpanzees)) and (ii) protect non-human primates against HIV-1 challenge. Applicants therefore asserted in their Response, that "given the state of the art at the time of the present invention, a person of skill in the art would not have been motivated by the Hung *et al.* reference or the Chanda *et al.* reference (which provide no *in vivo* data with regard to Ad7-HIV-1 *env* immunogenicity) to administer an Ad-*env* construct to a human to induce an immune response against HIV-1 infection. Furthermore, in the absence of Applicants' data (summarized above), one of skill would not have had a reasonable expectation of success based on the disclosure of either the Hung *et al.* reference or the Chanda *et al.* reference.

However, in the present Action, the Examiner contends that Applicants' arguments have been considered, but are "not found persuasive for the following reason(s):"

> i) In response to Applicants' "obvious to try" argument, Applicant is reminded that a prima facie showing of obviousness is based upon what the disclosure taken as a whole would suggest to one of skill in the art. In re McLaughlin, 170 U.S.P.Q. 209 (C.C.P.A 1971). The reference is evaluated by what it suggest to one versed in the art, rather than by its specific disclosure. In re Bozek, 163 U.S.P.Q. 545 (C.C.P.A. 1969). Moreover, in the instant, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to optimize the immunization regimen, i.e., vaccine formulation, dosage, routes of immunization, etc., to produce a strong immune response.
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> ii) Additionally, while Applicant is correct to note that neither Hung et al. nor Chanda et al. perform similar study in dogs with the Ad7-env constructs; however, such performance is not required of Hung et al. and Chanda et al. In the instant, Hung et al. and Chanda et al. clearly teach that the vector constructs are viable in vivo. Thus, the administration of a vector construct that expresses an HIV glycoprotein would necessarily invoke an immune response against an HIV because it is well known in the HIV art that HIV-1 envelope glycoprotein is highly immunogenic. A true mimic of the envelope would necessarily induce an immune response against HIV. Furthermore, Applicant is reminded that patentability determination is not made solely on the basis of the first to invent. Ergo, Applicant's proclamation that Applicant is the first to demonstrate protection of non-human primates against HIV-1 challenge is moot. In the instant, Hung et al. and Chanda et al. teach the composition employed in the claimed method, demonstrates that the vector construct is viable, and suggests the use of the composition to induce an immune response against HIV.

Applicants first wish to reiterate that the "obvious-to-try" rejection was formulated and presented by the Examiner, wherein the Examiner repeatedly stated that a person of skill in the art would have been motivated by the teachings of Hung *et al.* and/or Chanda *et al.* to **experiment** with various methodologies to arrive at the present invention. Applicants' maintain their position that an "obvious-to-try" rejection is not the standard for obviousness under 35 U.S.C. § 103. "Obvious-to-try has long been held not to constitute obviousness". *In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).*

> An obvious-to-try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co., 902 F.2d 943, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).*

More specifically, as was stated in *In re Dow Chemical*, 5 USPQ2d 1529, 1532 (Fed.Cir. 1988), "obvious to experiment" is not an appropriate test of obviousness: "The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a teaching or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."

Applicants further contend that the Examiner's rationale for rejecting the claimed invention as obvious under 35 U.S.C. § 103 (*i.e.*, the present rejection), contradicts the Examiner's position taken in a previous Official Action mailed March 19, 2004, wherein the claimed invention was rejected under 35 U.S.C. §112, first paragraph, for not complying with the enablement requirement. More specifically, the Official Action mailed March 19, 2004, rejected the claims of the invention for lack of enablement because Applicants' allegedly had "not provided any convincing evidence that their immunogenic composition was useful" and had "not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation". The March 19, 2004 Action concluded, "Thus, it is clear from the evidence of" the art, "that

the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success". Applicants' filed a Response to Official Action on June 18, 2004, traversing the enablement rejection under 35 U.S.C. §112, first paragraph, which was subsequently withdrawn in the Official Action mailed September 22, 2004.

However, the present Action insists that the claimed prime-boost methodology is predictable and obvious because "the administration of a vector construct that expresses an HIV glycoprotein would necessarily invoke an immune response against an HIV because it is well known in the HIV art that HIV-1 envelope glycoprotein is highly immunogenic". The Action continues, stating that the presently claimed prime-boost methods are obvious because "Hung et al. and Chanda et al. teach the composition employed in the claimed method, demonstrate[s] that the vector construct is viable, and suggest[s] the use of the composition to induce an immune response against HIV". Applicants respectfully disagree.

The claims of the present invention are directed to method for producing an immune response against HIV-1 infection in a human comprising the steps of (1) administering to the human an immunogenic composition comprising an intranasal or an intramuscular dosage of a recombinant adenovirus comprising an expression cassette containing a promoter, a nucleic acid sequence encoding the HIV-1 gp160 or gp120 polypeptide sequence and a polyadenylation signal sequence and (2) administering to the human one or more intranasal or intramuscular booster dosages of the recombinant adenovirus.

Contrary to the allegations set forth in the present Action, Applicants contend that given the state of the art at the time of the present invention, a person of skill in the art would not have been motivated by the Hung *et al.* reference or the Chanda *et al.* reference to administer an Ad-*env* construct to a human to induce an immune response against HIV-1 infection nor would the skilled artisan have had a reasonable expectation of success based on the disclosure of either the Hung *et al.* reference or the Chanda *et al.* reference. Applicants submit that absent the teachings of the present invention, which include both dog and non human primate (*i.e.*, chimpanzee) immunogenicity data demonstrating immune responses against HIV-1, a person of skill in the art, at the time the present application was

filed (*i.e.*, 1992), would not have found the presently claimed invention obvious. Applicants therefore respectfully request withdrawal of the rejection of claims 26 and 28-40 under 35 U.S.C. § 103.

It is Applicants' belief that claims 26 and 28-40 are in condition for allowance, and action towards that effect is respectfully requested. If there are any matters which may be resolved or clarified through a telephone interview, the Examiner is requested to contact the undersigned Agent at the number indicated.

The notice set a three-month period to comply, to and including July 21, 2005. Applicants respectfully request herewith, a one-month extension of time, to and including August 21, 2005. The Commissioner is authorized to deduct the fee of $120.00 for a one-month extension of time (37 C.F.R. § 1.17(a)(1)) from Deposit Account No. 01-1425. Thus, this response is believed to be timely filed.

Should any additional fees be deemed necessary, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-1425.

Respectfully submitted,

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